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Development of Locomotor Activity of Rat Pups in Figure-Eight Mazes

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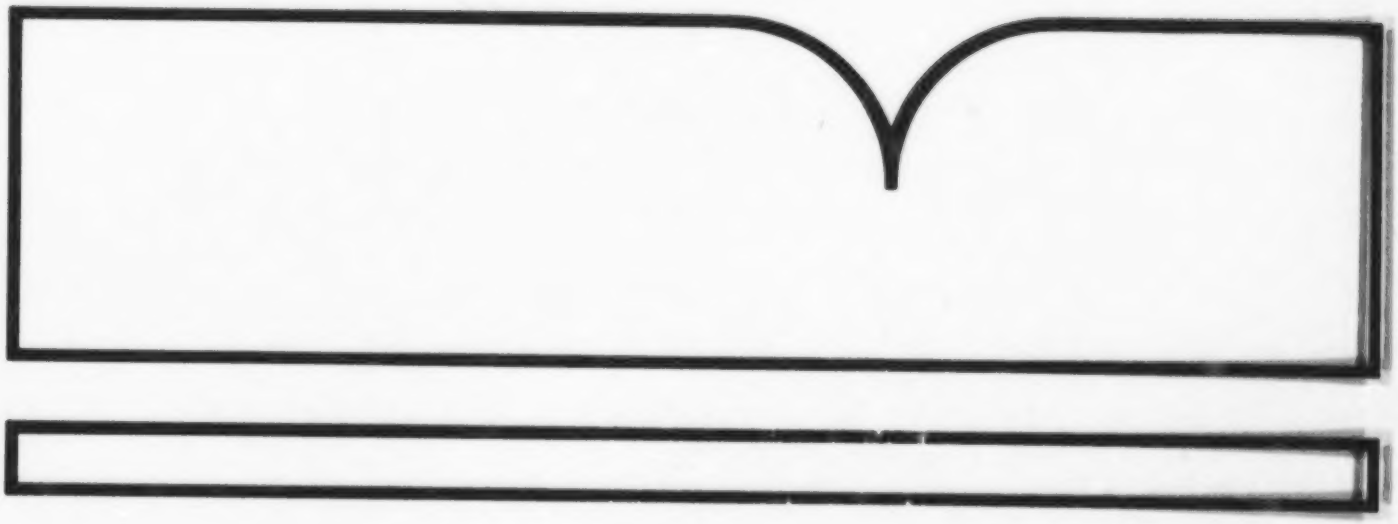

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16. ABSTRACT

In a series of four experiments, social and experiential factors that influence the development of motor activity in rat pups were examined. Motor activity was monitored from postnatal days 13 to 21 as photocell interruptions in figure-eight mazes and comparisons were made between (1) pups maintained in a next box containing a dam and siblings and allowed access to the maze for 23 hr/day, (2) pups tested daily for 1 hr/day vs. pups tested only on postnatal days 15, 18, or 21, (3) pups tested daily for either 5 min, 30 min, or 1 hr/day, and (4) pups tested daily for 30 min/day either singly in a maze, paired with a littermate, or paired with an anesthetized pup of the same age. A monotonic increase in activity was seen for nest-box testing, minimal developmental change was seen for pups tested on only a single day or for pups tested with an anesthetized pup, whereas all other groups showed an inverted U-shaped profile of activity which was influenced by the duration of testing and/or the presence of a littermate. These data emphasize the relevance of environmental factors as determinants of preweaning behavior.

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Development of Locomotor Activity of Rat Pups in Figure-Eight Mazes

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In a series of four experiments, social and experiential factors that influence the development of motor activity in rat pups were examined. Motor activity was monitored from postnatal Days 13 to 21 as photocell interruptions in figure-eight mazes and comparisons were made between (1) pups maintained in a nest box containing a dam and siblings and allowed access to the maze for 23 hr/day, (2) pups tested daily for 1 hr/day vs pups tested only on postnatal Days 15, 18, or 21, (3) pups tested daily for either 5 min, 30 min, or 1 hr/day, and (4) pups tested daily for 30 min/day either singly in a maze, paired with a littermate, or paired with an anesthetized pup of the same age. A monotonic increase in activity was seen for nest-box testing, minimal developmental change was seen for pups tested on only a single day or for pups tested with an anesthetized pup, whereas all other groups showed an inverted U-shaped profile of activity which was influenced by the duration of testing and/or the presence of a littermate. These data emphasize the relevance of environmental factors as determinants of preweaning behavior.

Motor activity is frequently used for behavioral evaluation of alterations in nervous system development. Preweaning evaluation of locomotor activity is relevant since neurotoxicants such as 6-hydroxydopamine produce juvenile hyperactivity that declines as the animals mature (Erinoff, MacPhail, Heller, & Seiden, 1979). However, components of motor activity (e.g., pivoting, crawling, walking, and running) show different patterns of development (Altman & Sudarshan, 1975; Bolles & Woods, 1964), and studies that record the ontogeny of different motor behaviors may report different findings. In addition, the type of activity that is measured and the complexity of the test environment affect measurements of locomotor activity (Reiter & MacPhail, 1982). Testing of locomotor activity in seminaturalistic environments such as burrows and nest boxes, in which pups are housed with the dam and siblings, differs from that in a variety of open-field situations where pups are tested apart from the nest area. These two test situations measure aspects of behavior which may be differentially affected by developmental insult.

Although pups develop the motor coordination required for ambulation by postnatal Day (PND) 10 (Bolles & Woods, 1964), emergence from a nest area occurs considerably

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later. Rat pups emerge from nest boxes between PND 19 and 20 when observed in indoor burrows (Galef & Clark, 1971). In figure-eight mazes, pups emerged from a nest box between PND 15–17 (Norton, Culver, & Mullenix, 1975; Reiter, Heavner, Dean, & Ruppert, 1981). Similar findings have been reported for emergence from a nest box into a small open field (Crofton, Taylor, Bull, Sivulka, & Lutkenhoff, 1980). Factors that constrain the activity of pups include intervention by the dam (Brewster & Leon, 1980; Smith & Berkson, 1973) as well as sibling-directed behaviors such as huddling (Alberts, 1978a). Gradual emergence from the nest is followed by a linear increase in locomotor activity that contrasts with the development of locomotor activity of rat pups tested in a novel environment. Motor activity can be assessed at a much earlier age, for example, when homing is used as a motivation. Pups orient to the home cage by PND 3 and, by PND 13, pups move from a neutral chamber to the home cage in less than 1 min (Altman, Brunner, Buluta, & Sudarshan, 1974). Campbell, Lytle, and Fibiger (1969) describe a peak in behavioral activity at the end of the second postnatal week, a finding that has been corroborated in several laboratories (Buelke-Sam, Sullivan, Kimmel, & Nelson, 1984; Erinoff et al., 1979; Oakley & Plotkin, 1975; Melberg, Ahlenius, Engel, & Lundborg, 1976).

This difference between the linear development of motor activity in seminaturalistic environments and the earlier onset and peak in activity of isolated pups could be due to several factors. The tendency of rat pups to remain in a huddle within the nest (Alberts, 1978a) or to remain in contact with an anesthetized conspecific when tested in isolation (Randall & Campbell, 1976) clearly demonstrates that social factors can influence the activity of preweaning animals regardless of test environment. Furthermore, different developmental trends have been reported for locomotor activity in stabilimeter cages, photocell chambers, open fields, and avoidance conditioning chambers (see Bauer, 1982).

In the present experiments, we used figure-eight mazes to address several questions regarding the influence of the dam and littermates (social factors) and the role of testing itself (experiential factors) on the development of locomotor activity in rat pups. Figure-eight mazes, designed by Norton and colleagues (Norton et al., 1975), allow a direct comparison of the development of activity under conditions comparable to those of a seminaturalistic environment (referred to as nest-box testing) and brief periods of testing (referred to as short-term testing). Since our aim is to use these procedures to investigate the effects of neurotoxicants on the development of motor activity, we focused on testing conditions that would be practical for testing brain-damaged pups and that would minimize separation from the dam.

General Methods

Long-Evans female rats (Charles River) were obtained 2 days after mating and individually housed in cages measuring 45 × 24 × 20 cm with pine shavings used as bedding material. Animals were maintained on a 12:12 light/dark cycle in an animal facility in which air temperature (22°C ± 2) and humidity (50% ± 10) were controlled. A reversed light:dark cycle with lights on at 2200 hours was used for Experiment II; for other experiments, lights came on at 1800 hours. Purina Lab Chow and water were available ad libitum throughout the experiments. One day after parturition (day of birth = PND 0), litters were randomized and each dam was assigned four male and four female pups. Pups were tattooed on a paw to provide unique identification within a litter (Avery & Spyker, 1977).

Motor activity was monitored in figure-eight mazes from PND 13–21. The maze is a series of interconnected alleys (10 × 10 cm) converging on a central arena and covered

by transparent acrylic plastic (Norton et al., 1975; Reiter, Anderson, Laskey, & Cahill, 1975). Activity was detected by eight phototransistor/photodiode pairs distributed throughout the maze (Fig. 1). The wire-screen floor of the maze rested 4 cm above a pan of pine shavings which were not changed for the duration of the experiment. Mazes ($N = 8$) were housed in a sound-attenuated room maintained on the same light:dark cycle as the animal room; dim illumination was provided for testing during the nocturnal phase by red incandescent bulbs. Data were analyzed using programs on the Biomedical Data Program (BMDP-4V) and the Statistical Analysis System (SAS). For all statistical tests, values greater than the critical value at $p < .05$ were accepted as significant.

For animals repeatedly tested from PND 13–21, a repeated-measures ANOVA was conducted using sex as the between animal factor; age and age × sex interactions were within animal factors. For independent groups of animals tested on PND 15, 18, or 21, a two-factor ANOVA (using age and sex) was performed. For habituation, activity counts for each 5-min interval were analyzed using repeated-measures ANOVA with sex as a between animal factor and time interval as the within animal factor.

Experiment I

Previous experiments have shown that emergence of pups from a nest box into the figure-eight maze occurred between PND 15–17 (Norton et al., 1975), and activity increased tenfold between PND 17–21 (Reiter et al., 1981). This developmental pattern was seen when both the dam and pups had access to the maze (Norton et al., 1975) and when the dam was confined to the nest box (Reiter et al., 1981). In both experiments, however, litter size was reduced to three to four pups, which can prolong maternal litter proximity during the third postnatal week (Grota & Ader, 1969). In the present experiment, we determined whether the same pattern of delayed emergence and development of activity would be observed for litters of seven to eight pups. In addition, direct observations of the number of pups in the mazes were made at several times during the diurnal period to confirm the age at emergence.

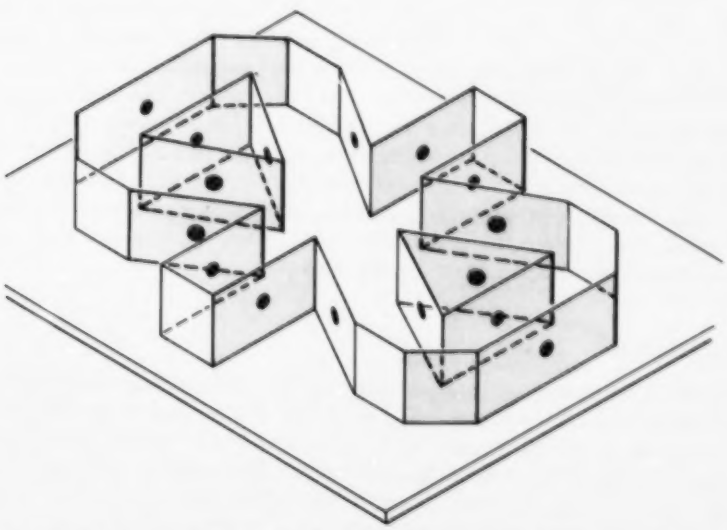

Fig. 1. Figure-eight maze. The location of photocells ($N = 8$) that detect motor activity is indicated by dark circles. (Reprinted from Ruppert, Walsh, Reiter, & Dyer, 1982.)

Methods

On PND 12, a dam and pups ($N = 8$ dams with 7–8 pups/litter) were housed in a nest box (20 × 20 × 10 cm) attached to the front alley of a maze. Food, water, and pine shavings for bedding material were available ad libitum. A small hole (2 × 3 cm) allowed pups access to the maze but confined the dam within the nest box. From PND 13–21, activity of pups in the mazes was recorded for 23 hr/day from 1000 to 0900 hours, with the remaining hour used to clean the nest boxes and test the photocells. In addition, the number of pups outside the nest box (i.e., in the maze) was observed 5 min, 30 min, 1 hr, and 23 hr after the start of each session. Because of equipment malfunction, photocell counts were lost for PND 20.

Results

Pups were inactive in the maze from PND 13 to 15, and motor activity rapidly increased from PND 16 to 21 (Fig. 2); this was seen as an effect of age on activity [$F(7,42) = 71.74$, $p < .001$]. Table 1 indicates the number of pups that were in the maze at each observation time. Dams actively prevented younger pups from leaving the nest box by lying in front of the exit or by poking their heads through the exit hole. By PND 18, a burst of activity occurred 5 min after the beginning of the session (1005 hours), but pups quickly returned to the nest box and resumed suckling. Not until PND 20 and 21 did pups remain active in the maze at other observation times.

Discussion

Motor activity of pups residing in a nest box with a dam and siblings showed a continuous increase during the preweaning period. This monotonic increase in activity agrees with previous data from figure-eight mazes; neither testing litters of seven or eight versus three or four (Norton et al., 1975; Reiter et al., 1981), monitoring only the activity of pups versus the dam and pups (Norton et al., 1975), or beginning testing on PND 13 vs PND 2 (Norton et al., 1975) or PND 15 (Reiter et al., 1981) markedly affected this development. Direct observations of the location of pups confirmed this delayed emergence from the nest box and indicated that this was at least partially accounted for by the behavior of the dam in restricting the passage of pups into the maze. Motor activity outside the nest area was initially constrained not only by the dam but also by the tendency of pups to return to the nest box after brief periods of exploration. This developmental profile contrasts with the peak in activity at the end of the second postnatal week described by Campbell et al. (1969). In the following experiments, we examined social and experiential factors which determine this differential profile.

Experiment II

A peak in preweaning activity was originally described for pups removed from the nest and tested individually (Campbell et al., 1969). The purpose of the second experiment was to assess the development of locomotor activity in figure-eight mazes for rat pups housed in standard laboratory cages and tested individually for 1 hr/day in the maze, i.e., short-term testing. If the test apparatus itself is the major determinant of activity, then a monotonic increase would be seen both for nest-box testing and short-term testing. If the conditions of testing are the major determinant of motor activity, then an earlier onset and perhaps a peak of activity would be seen for pups tested singly. Since the

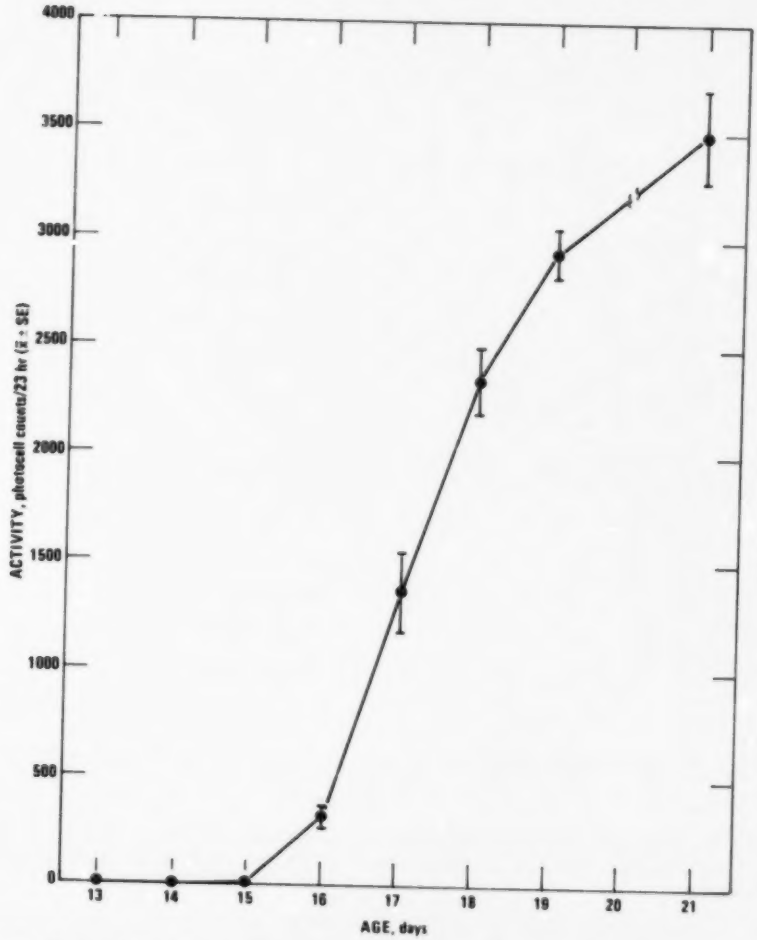

Fig. 2. Preweaning motor activity of rat pups emerging from the nest box from PND 13 to 21. Data are presented as photocell counts ($\bar{X} \pm$ SE) for 23 hr on each day of testing (Experiment I).

TABLE 1. Emergence from the Nest Box: Number of Pups Outside the Nest Box as a Function of Time (Total N = 61).

	Time (hours)			
PND	1005 (5 min)	1030 (30 min)	1100 (1 hr)	0900 (23 hr)
13	0	0	0	0
14	0	0	0	0
15	0	0	0	0
16	0	0	0	0
17	5	1	0	7
18	29	2	2	3
19	32	3	3	9
20	24	7	11	30
21	34	16	15	25

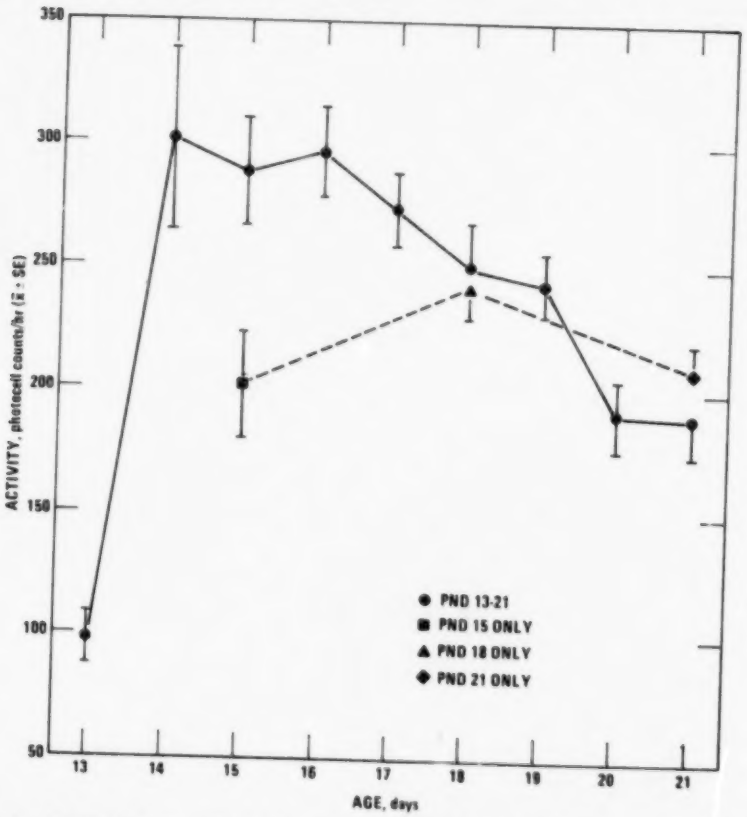

Fig. 3. Preweaning motor activity of rat pups tested repeatedly from PND 13 to 21 or only on PND 15, 18, or 21. Data are presented as photocell counts ($\bar{X} \pm$ SE) for the 1-hr session on each day of testing (Experiment II).

amount of testing can influence the development of activity (Moorcroft, Lytle, & Campbell, 1971; Nagy & Ritter, 1976), a comparison was made between pups repeatedly tested and those tested only once (naive animals).

Methods

Pups were tested individually in a maze for 1 hr either daily from PND 13–21, or only on PND 15, 18, or 21. One male and one female pup from each of the ten litters were assigned to each of the four groups.

Results

For pups repeatedly tested from PND 13 to 21, the developmental profile of activity was an inverted U-shaped function (Fig. 3); this was seen as an effect of age [$F(8,11) = 35.12$, $p < .001$]. There was a marginal effect of sex with males more active

than females [$F(1,18) = 4.55, p < .05$], but no interaction of sex with age. From PND 13 to 15, habituation of activity was minimal during the 1-hr period (Fig. 4). The overall activity level increased from PND 13 to 15 by 66%. A peak in initial 5-min activity occurred on PND 16, and by this time, pups began to show substantial within-session habituation, with photocell counts at later intervals lower than those at earlier intervals.

For naive pups, there was no effect of age on activity (Fig. 3) as indicated by a flat developmental curve, and no significant effect of sex. There was an interaction of age × time interval [$F(22,86) = 5.51, p < .001$] indicating that habituation was not uniform across age for naive pups. Pups tested on PND 15 did not habituate within the test session, whereas pups tested on PND 18 or 21 did show within-session habituation (Fig. 4).

Discussion

These data, which indicate a difference in the development of motor activity between repeatedly tested and naive pups, contrast with the monotonic increase in activity in figure-eight mazes during nest-box testing. Therefore, the conditions of testing, not the configuration of the apparatus, were a major influence on the developmental pattern of activity.

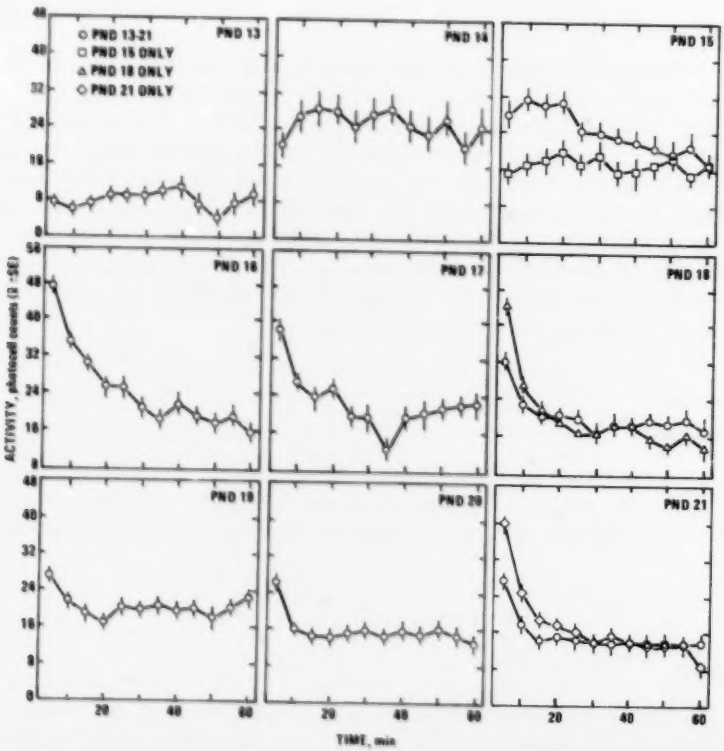

Fig. 4. Habituation of motor activity in figure-eight mazes for rat pups repeatedly tested from PND 13 to 21 or only on PND 15, 18, or 21. Data are presented as photocell counts ($\bar{X} \pm$ SE) for 5-min intervals during the 1-hr session on each day of testing (Experiment II).

With repeated short-term testing during the preweaning period, habituation developed both within a day and across days of testing. The most dramatic display of within-session habituation occured on PND 16 in conjunction with the highest peak in initial 5-min activity. Within-session habituation was not present for naive pups tested on PND 15 but was evident for naive pups tested on PND 18 or PND 21. Therefore, the development of habituation occurred in the absence of previous experience in the maze. These data are in agreement with previous studies which have shown that habituation of activity (Bronstein, Neiman, Wolkoff, & Levine, 1974) or exploratory head poking (Feigley, Parsons, Hamilton, & Spear, 1972; Williams, Hamilton, & Carlton, 1975) did not develop within a test session on PND 15, but was present by PND 18 (Feigley et al., 1972).

Differences in activity between repeatedly tested and naive pups were seen on PND 15, 18, and 21. Testing on PND 13 and 14 "sensitized" pups so their overall activity was higher than that of naive pups on PND 15. Similarly, mouse pups tested daily from PND 9–13 were reported to be more active on PND 11 and 13 than naive pups tested on those days (Nagy & Ritter, 1976). By PND 18 and 21, between-session habituation accounts for lower initial activity in repeatedly tested pups compared with naive pups.

Experiment III

The difference in the development of activity between nest-box testing (Experiment I) and short-term testing (Experiment II) could reflect several factors, including the degree of familiarity with the apparatus. For short-term testing, activity of naive pups (for which the maze was a novel environment) differed from that of repeatedly-tested animals: activity of naive animals on PND 15 was lower than that of pups with previous experience in the maze. In this third experiment, we varied the amount of daily testing, and thus familiarity with the maze, to determine how repeated-test experience contributes to the developmental profile of activity. Test durations were chosen to provide experience ranging from minimal familiarity (5 min/day) to test experience comparable to that of repeatedly-tested pups in the previous experiment.

Methods

Pups from ten litters (N = 7–8 pups/litter) were tested individually in a maze daily from PND 13–21. One male and one female pup from each litter were assigned to be tested for either 5 min, 30 min, or 1 hr each day; the remaining 1–2 pups/litter were not tested.

Results

Regardless of the duration of daily testing (from 5 min to 1 hr), an inverted U-shaped function was obtained (Fig. 5); this was seen as an effect of age on activity for the three groups [$F(8,11) = 39.07, 7.81, 12.97$, respectively; p's $< .001$]. Comparing the initial 5-min activity for all groups (Fig. 6), there was an age × group interaction [$F(16,94) = 2.35$; $p < .006$]. Initial 5-min activity was lower on PND 14 for pups

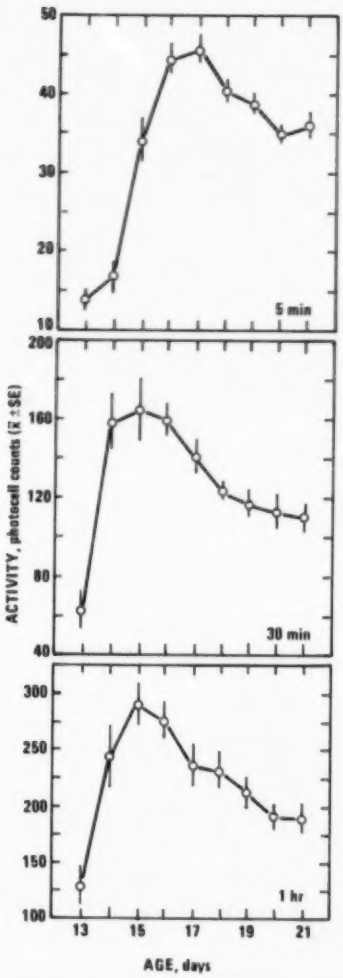

Fig. 5. Preweaning motor activity of rat pups tested from PND 13 to 21 for 5 min, 30 min, or 1 hr each day. Data are presented as photocell counts ($\bar{X} \pm$ SE) on each day of testing. Note the difference in scale for the three graphs (Experiment III).

tested for only 5 min/day compared with pups tested for 30 min or 1 hr. From PND 17 to 19, initial 5-min activity was lowest for pups tested the longest.

Discussion

For pups tested for 5 min, 30 min, or 1 hr, familiarity with the apparatus differed, yet the profile of activity was similar. Pups in all groups showed a peak in activity on approximately PND 15 followed by a gradual decline. Therefore, 5 min of testing per day was sufficient for pups to become familiar with the maze so that their activity on PND 15 differed from that of naive animals (Experiment II). It is interesting that a peak in activity was seen for pups separated from the dam for only 5 min each day,

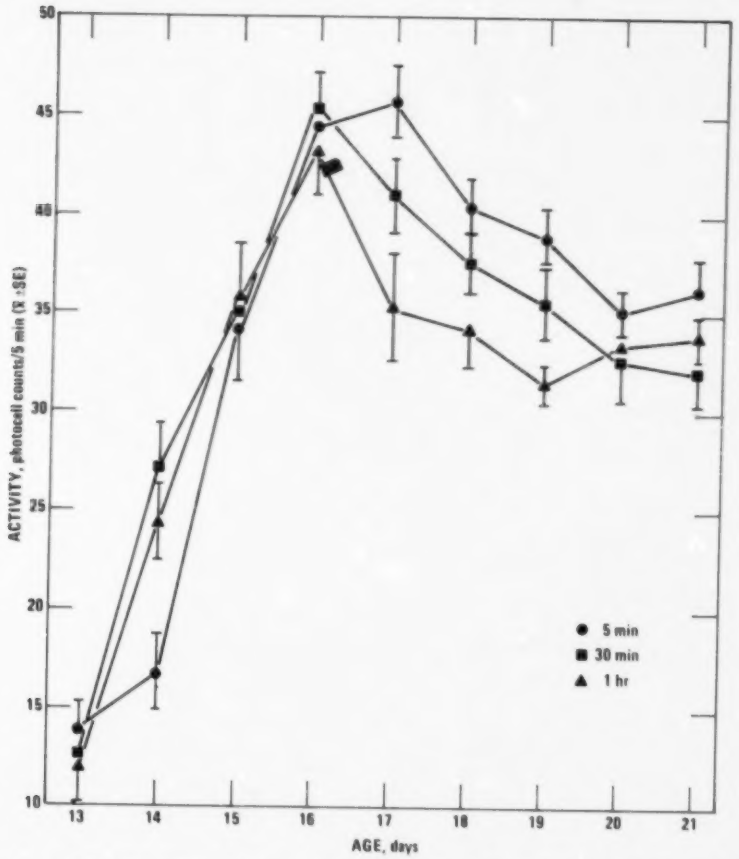

Fig. 6. Initial 5-min activity of rat pups tested from PND 13 to 21 for 5 min, 30 min, or 1 hr each day. Data are presented at photocell counts ($\bar{X} \pm$ SE) on each day of testing (Experiment III).

since it is unlikely that either starvation (Moorcroft, 1981) or hypothermia (Bronstein, Marcus & Hirsch, 1978) could account for this profile. The lower initial activity on PND 14 for pups tested for only 5 min agrees with data from Experiment II indicating that previous testing increased activity on PND 15. However, differences in activity between groups during the first 5 min of each test indicated that testing duration also influenced the developmental trends and that the influence of testing experience varied with age.

Experiment IV

Randall and Campbell (1976) have shown that the presence of a dam or siblings reduced the activity of pups on PND 15, while at this age, pups were more likely to follow a moving, anesthetized adult male than were either younger or older pups (Campbell & Randall, 1975). In the fourth experiment, we assessed the influence of a single littermate or an age-matched anesthetized pup on the development of activity. Since pups were the same age on each day of testing, the mobility or inactivity of "stimulus" pups was the critical dimension which varied between groups.

Methods

Pups were tested for 30 min/day from PND 13 to 21 singly in the maze, paired with a littermate of the same sex, or paired with an age-matched anesthetized pup. One male and one female pup from each of 10 litters were assigned to be tested singly, one pair of each sex was tested jointly from each litter, and the remaining male and female pup were tested with an anesthetized pup. Age-matched controls were anesthetized with ketamine (Bristol Laboratories, 1.0 ml/kg) and placed in the center of the maze. Activity of paired pups was divided by two for presentation and analysis of the data to make comparisons with the activity of pups tested singly.

Results

Both the amount of activity and the developmental profile differed for the three groups (Fig. 7). For total activity, there was a group × age interaction [$F(16,90) = 2.43$; $p < .004$]; therefore, simple main effects were examined. On PND 13 and 14, there was no difference in activity between the three groups, but from PND 15 to 21, there was a significant effect of group which varied with age. On PND 15 and 16, all

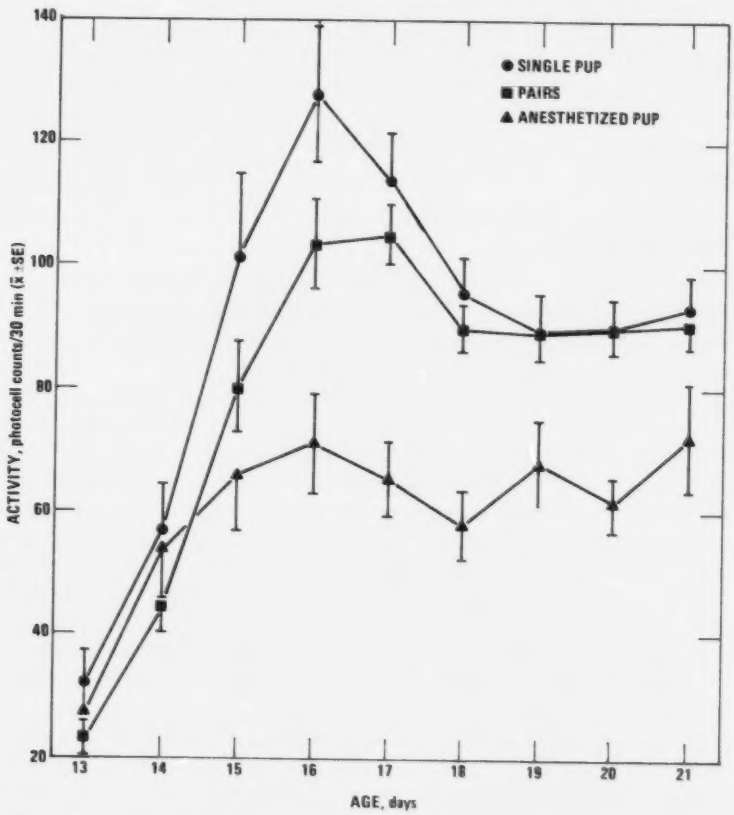

Fig. 7. Preweaning motor activity of rat pups tested from PND 13 to 21 either singly in a maze, paired with a littermate of the same sex, or paired with an anesthetized age-matched pup. Data are presented as photocell counts ($\bar{X} \pm$ SE) for the 30-min session on each day of testing (Experiment IV).

groups were different from each other, with singly tested pups more active than paired pups or pups matched with an anesthetized pup, which were least active. On PND 17–21, pups tested with an anesthetized pup were less active than both singly tested pups and pups tested in pairs.

Discussion

Campbell and colleagues have investigated similar social variables affecting the development of locomotor activity using more extended tests. The duration of their test sessions was generally 6–16 hr, and in some cases pups were adapted to the apparatus for 1 hr before observations were initiated. Despite this methodological difference and the difference in apparatus, our experiments are in agreement with the fact that isolated pups modify their activity in the presence of conspecifics. In figure-eight mazes, the activity profiles of littermate pairs or of pups tested with an anesthetized pup differed from that of pups tested singly.

In agreement with the findings of Randall and Campbell (1976), the presence of an anesthetized pup eliminated the peak in activity normally seen at the end of the second postnatal week. Their data indicated that the presence of two siblings would also attenuate the activity of a third pup; our data agree with this finding in that activity on PND 15 and 16 was attenuated for paired pups. This preference for contacting conspecifics is in agreement with the modulation of activity obtained in nest-box testing. For adult rats tested in groups, the activity of pairs is more than twice that of individual animals; this social facilitation consists of following, chasing, etc. (Norton, 1977). The activity of paired pups may more closely resemble the following behavior of pups toward a moving anesthetized adult (Campbell & Randall, 1975) than true social interaction.

General Discussion

The major conclusion of these experiments is that the development profile of motor activity in rat pups is determined primarily by the conditions of testing and not by the apparatus *per se*. Although pups were tested in figure-eight mazes in all four experiments, social and experiential variables produced systematic changes in the behavior of pups. This was evident in the very different profiles of activity of pups tested within the litter unit (Experiment I), singly (Experiments II and III) or paired with another pup (Experiment IV). This differing response profile emphasizes the role of the dam and littermates in regulating the behavior of altricial pups (Alberts, 1978b; Hofer & Grabie, 1971). By PND 14 and 15, the dam remains away from the litter for 30–60-min periods throughout the day (Hofer, 1975), so that the removal of pups from the home cage for a testing maximum of 1 hr/day was not an unusual deprivation. This is advantageous for the testing of brain-damaged pups, who may be less physically mature than control pups.

A major unresolved issue is the role of testing experience in the development of activity. In figure-eight mazes, the amount of previous testing determines the level of activity on PND 15 and 16. Pups tested on either PND 15, 18, or 21 in figure-eight mazes did not show an effect of age on total activity (Experiment II), but as little as 5 min of testing per day (Experiment III) was sufficient to demonstrate an increase in activity on PND 15 and 16. In motrons, a peak in activity was seen on PND 15 for rat pups tested daily, but this function was not obtained when pups were tested every third day (MacPhail, personal communication). In contrast, experience in a stabilimeter was not necessary to observe a peak in arousal during the second postnatal week (Campbell et al., 1969), and recently Buelke-Sam et al. (1984) reported a similar peak in activity

on PND 16 for pups tested in photocell chambers at 2- or 4-day intervals. It is possible that differences in developmental trends which have been attributed to the test apparatus (see Bauer, 1982) may actually reflect the frequency of testing in different experiments. Such a finding would redirect inquiry to the characteristics of a particular test apparatus which interact with experience.

The differing profile of activity during nest-box testing versus short-term testing can be informative for assessment of behavior after developmental insult. Rat pups exposed to a neurotoxic organotin compound on PND 5 were hypoactive in figure-eight mazes during nest-box testing (Reiter et al., 1981) but hyperactive during short-term testing (Ruppert, Dean, and Reiter, 1984). Therefore, this paradigm provides the potential for assessing how the expression of brain damage is modulated by the postnatal environment.

Notes

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